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GLOBAL STABILITY OF A DELAYED HIV-1 DYNAMICS MODEL WITH SATURATION RESPONSE WITH CURE RATE, ABSORPTION EFFECT AND TWO TIME DELAYS

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Abstract. In this paper, we proposed a new HIV-1 infection model with saturation infection rate by incorporating, cure rate, absorption effect, and two-time delays namely intracellular time delay that representing the time viral passage into a target cell and creation of new infectious particles and maturation time delay representing the required time for newly produce virus to mature and the infect the susceptible cell. The mathematical investigation shows that the basic reproduction number R_0 of the model totally decides the steadiness properties. Utilizing the characteristic equation of the model and Routh-Hurwitz steadiness basis, we affirmed that the infection-free equilibrium and the chronic disease equilibrium are locally asymptotically steady in case $R_0 \leq 1$ and $R_0 > 1$, individually. If $R_0 \leq 1$, using the appropriate Lyapunov functions and LaSalle's invariance principle, it has been shown that the infection-free equilibrium of the model is globally asymptotically stable. If $R_0 > 1$ the model is persistent. Conversely, if $R_0 > 1$, the infection-free equilibrium is unstable and a unique chronic infection equilibrium exists. We show that, if $R_0 > 1$, the chronic infection is globally asymptotically stable. Moreover, numerical simulations are performed to verify the theoretical results.

Keywords: global stability; permanence; cure rate; absorption effect; intracellular and maturation time delays.

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1. INTRODUCTION

HIV is called human immunodeficiency infection, taints and annihilates the cells of the human resistant framework, challenging it to battle off other illnesses. When HIV severely weakens the human immune system, it causes acquired immunodeficiency syndrome (AIDS) [1]. HIV contamination happens through the exchange of blood, bosom milk, vaginal liquid, semen, or pre-ejaculation. In these body fluids, HIV may exist in the form as free-virus and virus within the infected cells. HIV attacks to the immune system of the body, which consists of a variety of biological structures to prevent or control a variety of infections and diseases.

$CD4^+$T cells are focal middle mediators of the immune system in people, critically organizing cellular and humoral immune reactions against infections. The use of $CD4^+$T lymphocytes in the fight against infections is reduced because HIV only infects $CD4^+$T lymphocytes, which make up a large portion of white blood cells [2]. Therefore, if the infected body is not given external treatment, the amount of $CD4^+$T in the human body can be drastically reduced and it may increasing trend to receive the associated diseases. An opportunistic infection occurs when a certain number of $CD4^+$T cells are destroyed, resulting in weakened immune systems. Therefore, if not treated with HIV drugs, HIV can gradually destroy the immune system and develop into the acquired immunodeficiency syndrome (AIDS), which is the advanced stage of HIV infection (see [3, 4]).

Current statistics published by the World Health Organization indicate that HIV remains as a major global public health problem. Certain antiretroviral (ARV) drugs are currently available to help the immune system fight off HIV infection. Protease Inhibitors (PIs), is one of chemotherapy drugs that inhibit virus production from actively infected $CD4^+$T cells. Reverse transcriptase inhibitors (RTIs) are another chemotherapy that opposes the conversion of the virus's RNA into DNA (reverse transcription), so that the viral population will be low and the $CD4^+$T count will high and the host can survive (see [5, 6]). Even though HIV treatment and prevention have made significant progress, appropriate or relevant drug therapy must still be promoted. The dynamics of HIV infection, its progression, and the immune system's cooperation with HIV can all be studied with the help of mathematical modeling.

Bonhoeffer and Nowak proposed the fundamental virus dynamics model (1.1) in section [7], and Korobeinikov performed the model's entire theoretical calculation in [8].

$$\begin{aligned} \dot{x}(t) &= \lambda - \beta x(t)v(t) - dx(t), \\ \dot{y}(t) &= \beta x(t)v(t) - py(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{1.1}$$

Where, $x(t)$ and $y(t)$ denote the densities of uninfected cells and infected cells which have capability to produce virus at time t, respectively. $v(t)$ is free virus at time t. All parameters of model (1.1) are assumed to be positive constants, and the biological meanings of them are as follows. The new uninfected cells generating rate is denoted by parameter λ. The parameters d and β are the natural death rate of uninfected cells and the rate of infection, respectively. The infected cells produce new viruses at a rate of k throughout their lifetimes, with p representing the death rate of the infected cells as a result of the virus or the immune system. parameter u represent the cleaning rate of free virus from the system.

In model (1.1), the rate of disease infection per host and per virus is assumed to be a bilinear incidence rate, and virus particles produce virus immediately upon binding to a target cell without a time delay. The tests detailed in [9] unequivocally recommended that the contamination pace of microparasitic diseases is a rising capability of the parasite portion, and is normally sigmoidal in shape (see e.g [10]). In [11], it has been demonstrated biologically that there is a delay known as the intracellular time delay between the time a virus enters a target cell and the time it takes that infected cell to produce another virus. Therefore, researchers are motivated to propose and develop the mathematical dynamics models by introducing time delays and the different functional responses instead of the bilinear functional response (see e.g.[12, 13, 14]).

Li-Ming et al. in [13] Have examined the HIV-1 infection model using the Beddington-DeAngelis functional response and intracellular time delay, and they demonstrated that the system is permanent and infection equilibrium is globally asymptotically stable if the reproduction number is greater than one. In fact, when a pathogen enters into uninfected cells, the number of pathogens in the blood volume decreases, which is known as the retention impact or absorption effect (see e.g [14]). In [15], Pradeep and Ma have looked at a HIV-1 virus dynamics

model with an absorption effect, a Beddington-DeAngelis functional response, and an intracellular time delay. The authors have determined the local and global stability of the infection-free equilibrium by using Lyapunov method and determine only local stability of the chronic infection equilibrium and show that the stability properties are totally dependent on the reproduction number of the model. A HIV-1 model with double delays (intracellular deferral and immune delay) and infection depreciation term is proposed in [16]. The authors have done a total analytical calculation and numerical simulation. Further suggested that intracellular delay is more important than the immune delay.

In [17], Hattaf and Noura have considered the mathematical model with the general form of infection process by incorporating the cure rate and absorption effect without considering the delay terms. In this paper the authors have determined the stability of the disease free equilibrium by direct Lyapunov method and geometrical approach have used for chronic infection.

Geo and Ma [18], have considered the Mathematical dynamics model of HIV with apoptosis by incorporation intracellular time delay and considering the general nonlinear infection processes. The authors have determined that if the basic reproduction number of the model is less than unit, the infection-free equilibrium is globally asymptotically stable and global attractors if equal to unity. They further show that the system is permanent if the reproduction number greater than unity.

In [19], Zhuang and Zhu have suggested a model for the dynamics of HIV with cure rate. The authors have studied the existence of Hopf bifurcation by analysing the transcendental characteristic equation and used the Hopf bifurcation theory for global existence of bifurcating periodic solutions. Culshaw and Ruan have presented a mathematical model with intercellular time delay in [20] and the authors have discussed the effect of the time delay on the stability of the endemically infected equilibrium and they have given criteria to ensure the chronic infection is asymptotically stable for all delay.

A HIV-1 dynamics model by incorporating with both saturation infection rate and intracellular time delay has been proposed by Xu in [21]. The author has determined the local and global stability of the both infection-free equilibrium and a chronic-infection equilibrium of the model.

In addition, Xu conducted a comprehensive mathematical analysis of the HIV-1 infection model in [22], which included an intracellular delay and absorption effect.

The time required for the virus to ripen after the infected cells have replicated the new virus is known as the maturation time. A newly produced virus cannot attach directly to uninfected target cells without maturing biologically. A mathematical model in [23] has been presented by incorporating both intercellular time and maturation time and a thorough theoretical analysis has been performed to show the global stability of the model.

In [24], the authors present a mathematical model that incorporates an intracellular time delay, a maturation time delay, and an absorption effect. They also demonstrate that the model's equilibrium points are stable both locally and globally. Further researcher have shown that the system is permanent.

Inspired by the above researches, we can consider the following dynamic model of HIV infection together with the saturation infection rate by incorporating absorption effects, intercellular time delay, maturation time delay, and cure rate.

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \gamma y(t), \\ \dot{y}(t) &= \frac{\beta e^{-p\tau} x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - (p+\gamma)y(t), \\ \dot{v}(t) &= ke^{-u\sigma} y(t-\sigma) - uv(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}. \end{aligned} \tag{1.2}$$

where, $\tau \geq 0$ represent the intercellular time delays, the term $e^{-p\tau}$ is the probability of surviving from $t-\tau$ to t, $1/\alpha$ is half saturation constant, when the number of susceptible cells increases the inhibition effect from the behavioral change is measured by $1/(1+\alpha v)$ and the infectivity of the virus is measured by βv, $\sigma \geq 0$ present the maturity time delay, the term $e^{-u\sigma}$ present the probability of surviving from time $t-\sigma$ to t, γ is the cure rate of infected cells. In addition, it is presumptively assumed that all parameters are positive, and the remaining variables have the same biological significance as the models discussed earlier.

The remainder of the content of the paper is arranged as follows. Section 2 present the solution of system (1.2)'s positive, bounded, and limiting behavior. The existence of the unique equilibrium of the system (1.2), as well as the local and global stability of each equilibrium point, are all discussed in Section 3. In Section 4, the permanency of system (1.2) is discussed.

In Section 5, the numerical simulations of system (1.2) are discussed. Section 6 provides a discussion and conclusion.

2. PROPERTIES OF SOLUTION

Since the model depicts the growth of a cell population, we present the positivity and boundingness of model (1.2) solutions in this section. As a result, the cell numbers ought to remain fixed and not negative. The solutions' global presence is inferred by these properties.

2.1. Positivity and boundedness.

Let the initial condition of (1.2) is

$$x(\theta) = \psi_1(\theta), y(\theta) = \psi_2(\theta), v(\theta) = \psi_3(\theta), \quad \text{and} \quad \psi_i(\theta) \geq 0, i = 1,2,3. \tag{2.1}$$

where $\theta \in [-\zeta, 0]$, $\psi = (\psi_1(\theta), \psi_2(\theta), \psi_3(\theta)) \in C$, and $\zeta = max\{\tau, \sigma\}$. $C([-\zeta, \mathbb{R}^3_+])$ map the interval $[-\zeta, 0]$ into $\mathbb{R}^3_+$.

Theorem 2.1. *Let $(x(t), y(t), v(t))$ be the solution of the model (1.2) satisfy the initial condition (2.1), then the $x(t), y(t)$ and $v(t)$ are positive and ultimately bounded for all $t \geq 0$. Further we have*

(i) $w(t) \leq w(0) + \frac{\lambda}{\delta}$.

(ii) $v(t) \leq v(0) + \frac{ke^{-u\sigma}}{u}\|y\|_\infty$.

where $w(t) = x(t) + y(t) + \beta \int_{t-\tau}^{t} e^{-p(t-s)} \frac{x(s)v(s)}{1+\alpha v(s)} ds$, *and* $\delta = min\{d, p\}$.

Proof. To start with, we will confirm the solution of system (1.2) is positive. Using the constant variable formula, we get the following solution for the first and second equations of system (1.2).

$$x(t) = e^{-dt}\left[x(0)e^{-\int_0^t \frac{\beta v(\xi)}{1+\alpha v(\xi)} d\xi} + \int_0^t (\lambda + \gamma y(\eta)) e^{d\eta - \int_\eta^t \frac{\beta v(\xi)}{1+\alpha v(\xi)} d\xi} d\eta\right]. \tag{2.2}$$

$$y(t) = y(0)e^{-(p+\gamma)t} + \beta e^{-p\tau} \int_0^t \frac{x(\eta-\tau)v(\eta-\tau)}{1+\alpha v(\eta-\tau)} e^{-(p+\gamma)(t-\eta)} d\eta. \tag{2.3}$$

Let $t \in [0, \zeta]$, we have $(\eta - \tau) \in [-\zeta, 0]$ for all $\eta \in [0, \zeta]$. Then using the initial condition (2.1) and equation (2.2) and (2.3), we deduce that $x(t) \geq 0, y(t) \geq 0$ for $t \in [0, \zeta]$. This method can repeat on $[\zeta, 2\zeta]$ to show that $x(t)$ and $y(t)$ are non-negative, and then successive intervals $[n\zeta, (n+1)\zeta]$ for $n \geq 2$.

Next, we show that $v(t)$ is non-negative for $t > 0$. Assuming contrary, and considering $t_1 > 0$ be the first time such that $v(t_1) = 0$. Then by the third equation of the model (1.2) and the similar argument above we have $\dot{v}(t_1) = ke^{-n\sigma}y(t_1 - \sigma) > 0$, and hence we have $v(t) < 0$ for some $t \in (t_1 - \varepsilon, t_1)$ for sufficiently small $\varepsilon > 0$. This contradicts $v(t) > 0$ for $t \in [0, t_1]$. Therefore it follows that $v(t) > 0$ for $t > 0$. This confirms the positivity of the solution.

Next, we have to show that the model (1.2) has bounded solutions.

From the first and second equations of (1.2), we have

$$\dot{w}(t) = \lambda - dx(t) - py(t) - p\beta \int_{t-\tau}^{t} e^{-p(t-s)} \frac{x(s)v(s)}{1+\alpha v(s)} ds. \tag{2.4}$$

Equation (2.4) can be deduced as

$$w(t) \leq w(0)e^{-\delta t} + \frac{\lambda}{\delta}(1 - e^{-\delta t}). \tag{2.5}$$

As $1 - e^{-\delta t} \leq 1$ and $0 \leq e^{-\delta t} \leq 1$, we have (i).

The third equation of (1.2) can be simplify as

$$v(t) \leq v(0)e^{-ut} + ke^{-u\sigma} \int_0^t e^{u(s-t)} y(s - \sigma).ds \tag{2.6}$$

Then, we have

$$v(t) \leq v(0) + \frac{ke^{-u\sigma}}{u} \|y\|_\infty (1 - e^{-ut}). \tag{2.7}$$

Since $1 - e^{-ut} \leq 1$, from equation (2.7), we have (ii).

This confirms that the solutions of the model (1.2) are bounded. □

2.2. Limiting behavior of solution. It is important to focus our attention on the existence of solutions to the finite behavior of the dynamical model.

Proposition 2.2. *Let $X(t) = (x(t), y(t), v(t))$ be the solution of the model (1.2) subject to the initial condition (2.1), then the limit of $X(t)$ exists as $t \to +\infty$. Additionally, we have*

$$\lim_{t\to\infty} x(t) \leq \frac{\lambda}{d}, \tag{2.8}$$

$$\lim_{t\to\infty} y(t) \leq \frac{u\lambda(\lambda - d\lim_{t\to\infty} x(t))}{pud + (e^{p\tau} - 1)R_0(a+\delta)(ud + \beta\lambda)\lim_{t\to\infty} x(t)}, \tag{2.9}$$

$$\lim_{t\to\infty} v(t) \leq \frac{ke^{-u\sigma}}{u} \lim_{t\to\infty} y(t). \tag{2.10}$$

Proof. Let $z(t) = \beta \int_{t-\tau}^{t} e^{-p(t-s)} \frac{x(s)v(s)}{1+\alpha v(s)} ds$. Then adding the first and second equation of (1.2) and the derivative of $z(t)$, we have

$$\dot{x}(t) + dx(t) = \lambda - (\dot{y}(t) + py(t)) - (\dot{z}(t) + pz(t)). \tag{2.11}$$

Equation (2.11) can be derived in form

(2.12)
$$x(t) = (z(0)+y(0)+x(0))e^{-dt} - z(t) - y(t) + \frac{\lambda}{d}(1-e^{-dt}) + (d-p)\int_0^t (y(s)+z(s))e^{d(s-t)} ds.$$

If $d \geq p$, from Lemma 3.3 in [25] and equation (2.12), we have

$$\begin{aligned} \limsup_{t\to+\infty} x(t) &\leq \frac{\lambda}{d} - \frac{p}{d}\left(\limsup_{t\to+\infty} y(t) + \limsup_{t\to+\infty} z(t)\right), \\ \liminf_{t\to+\infty} x(t) &\geq \frac{\lambda}{d} - \frac{p}{d}\left(\liminf_{t\to+\infty} y(t) + \liminf_{t\to+\infty} z(t)\right). \end{aligned} \tag{2.13}$$

If $p \geq d$, using similar methods to get equation (2.12), we have

$$y(t) = (z(0)+y(0)+x(0))e^{-pt} - x(t) - z(t) + \frac{\lambda}{p}(1-e^{-pt}) + (p-d)\int_0^t e^{p(s-t)} x(s) ds, \tag{2.14}$$

and, using Lemma 3.3 in [25] and from equation (2.14), we get

$$\begin{aligned} \limsup_{t\to+\infty} y(t) &\leq \frac{\lambda}{p} - \frac{d}{p}\limsup_{t\to+\infty} x(t) - \limsup_{t\to+\infty} z(t), \\ \liminf_{t\to+\infty} y(t) &\geq \frac{\lambda}{p} - \frac{d}{p}\liminf_{t\to+\infty} x(t) - \liminf_{t\to+\infty} z(t). \end{aligned} \tag{2.15}$$

By comparing system (2.13) and (2.15), for the parameters $p > 0$, and $d > 0$, we have

$$\begin{aligned} \limsup_{t\to+\infty} x(t) &\leq \frac{\lambda}{d} - \frac{p}{d}\left(\limsup_{t\to+\infty} y(t) + \limsup_{t\to+\infty} z(t)\right), \\ \liminf_{t\to+\infty} x(t) &\geq \frac{\lambda}{d} - \frac{p}{d}\left(\liminf_{t\to+\infty} y(t) + \liminf_{t\to+\infty} z(t)\right). \end{aligned} \tag{2.16}$$

Then, from system (2.16), we have

$$\limsup_{t\to+\infty} x(t) - \liminf_{t\to+\infty} x(t) \leq \frac{p}{d}\left(\liminf_{t\to+\infty} y(t) - \limsup_{t\to+\infty} y(t)\right) + \frac{p}{d}\left(\liminf_{t\to+\infty} z(t) - \limsup_{t\to+\infty} z(t)\right).$$

Thus, easily we can prove that

$$\limsup_{t\to+\infty} x(t) = \liminf_{t\to+\infty} x(t), \quad \limsup_{t\to+\infty} y(t) = \liminf_{t\to+\infty} y(t), \quad \text{and} \quad \limsup_{t\to+\infty} z(t) = \liminf_{t\to+\infty} z(t).$$

Then, from (2.16), we have

$$\lim_{t\to+\infty} y(t) = \frac{\lambda}{p} - \frac{d}{p}\lim_{t\to+\infty} x(t) - \lim_{t\to+\infty} z(t). \tag{2.17}$$

Since $z(t) \geq 0$ and $y(t) \geq 0$ for all $t \geq 0$, from equation (2.17), we have (2.8).

From equation (2.6), we can easily deduce (2.10).

Since we have,

$$z(t) = \beta \int_0^\tau \frac{e^{-ps}x(t-s)v(t-s)}{1+\alpha v(t-s)}ds,$$

then,

$$\lim_{t\to+\infty} z(t) = \frac{\beta}{p}(1-e^{-p\tau})\lim_{t\to+\infty}\left(\frac{x(t)v(t)}{1+\alpha v(t)}\right).$$

Therefore, from equation (2.17), we obtain

$$\lim_{t\to+\infty} y(t) = \frac{\lambda}{p} - \frac{d}{p}\lim_{t\to+\infty} x(t) - \frac{\beta}{p}(1-e^{-p\tau})\lim_{t\to+\infty}\left(\frac{x(t)v(t)}{1+\alpha v(t)}\right). \tag{2.18}$$

Using (2.10) and (3.1), from equation (2.18), we can easily obtain (2.9). This implies that the solution of (1.2) extends for any $t > 0$. Consequently, the solutions of (1.2) exist globally. □

3. Model Analysis

In this section, we study the existence of the infection-free equilibrium point $E_f(x_0, y_0, v_0)$ and the chronic infection equilibrium point $E_{ch}(x_1, y_1, v_1)$ of model (1.2) and their stabilities.

3.1. Basic reproduction number. The average number of infected cells produced by one infected cell during the time of admixture when all cells are uninfected is referred to as the basic reproductive number. The similar approach that was provided in [26] can be used to determine the model reproduction number and which is denoted as R_0.

$$R_0 = \frac{\lambda\beta k e^{-u\sigma-p\tau}}{(p+\gamma)(ud+\lambda\beta)}, \tag{3.1}$$

where $\frac{1}{p+\gamma}$ represents the average length of time an infected cell can be expected to live that is less than $\frac{1}{p}$ because a portion of infected cells recover by removing all DNA from their nuclei at a rate γ [17]. The dynamics of the system are significantly influenced by R_0.

Theorem 3.1.

(i) If $R_0 \leq 1$, then model (1.2) has a unique infection free equilibrium of the form $E_f(\lambda/d,0,0)$.

(ii) if $R_0 > 1$, then model (1.2) has a unique chronic infection equilibrium of the form $E_{ch}(x_1,y_1,v_1)$ with $x_1 \in (0,\frac{\lambda}{d}), y_1 > 0$, and $v_1 > 0$.

Proof. For any equilibrium points, the following system of equations holds.

$$\lambda - dx - \frac{\beta xv}{1+\alpha v} + \gamma y = 0 \tag{3.2}$$

$$\frac{\beta e^{-p\tau} xv}{1+\alpha v} - (p+\gamma)y = 0 \tag{3.3}$$

$$ke^{-u\sigma} y - uv - \frac{\beta xv}{1+\alpha v} = 0 \tag{3.4}$$

Form the equations (3.2) and (3.3), we have $y = \dfrac{\lambda - dx}{pe^{p\tau} + (e^{p\tau}-1)\gamma} \geq 0$ implies that $x \leq \frac{\lambda}{d}$. Hence, there is no equilibrium point for the system if $x > \frac{\lambda}{d}$.

By direct calculation from the equations (3.2)-(3.4), it is easy to show that, if $R_0 > 1$, system (1.2) has a unique chronic infection equilibrium point $E_{ch}(x_1,y_1,v_1)$, where

$$x_1 = \frac{\lambda u(1+\alpha v_1)}{udR_0 + (R_0-1)\beta\lambda}, \qquad y_1 = \frac{\beta e^{-p\tau} x_1 v_1}{(1+\alpha v_1)(p+\gamma)},$$
$$v_1 = \frac{(p+\gamma)(ud+\beta\lambda)(R_0-1)}{u[p\beta + d\alpha(p+\gamma) + \gamma\beta(1-e^{-p\tau})]}. \tag{3.5}$$

Further, if $R_0 \leq 1$, from (3.5) and Theorem 2.1, we have a unique infection-free equilibrium point of model (1.2) is $E_f(\frac{\lambda}{d},0,0)$, which corresponds to the maximum level of healthy $CD4^+T$ cells in the body. □

3.2. Stability of the infection free equilibrium. In this subsection we discuss about the local stability of the infection free equilibrium point, $E_f(\lambda/d,0,0)$ by using then characteristic equation of model (1.2) and global stability of E_f through the application of appropriate Lyapunov functions and LaSalle's invariance principle.

Let $E(x,y,v)$ be an arbitrary equilibrium point. Then the characteristic equation of the system (1.2) about E is:

$$\begin{vmatrix} s+\dfrac{\beta v}{1+\alpha v}+d & -\gamma & \dfrac{\beta x}{(1+\alpha v)^2} \\ -\dfrac{\beta v e^{-p\tau-s\tau}}{1+\alpha v} & s+p+\gamma & -\dfrac{\beta x e^{-p\tau-s\tau}}{(1+\alpha v)^2} \\ \dfrac{\beta v}{1+\alpha v} & -ke^{-u\sigma-s\sigma} & s+u+\dfrac{\beta x}{(1+\alpha v)^2} \end{vmatrix} = 0. \tag{3.6}$$

Theorem 3.2. *For any $\tau \geq$ and $\sigma \geq 0$,*

(i) if $R_0 < 1$, then E_f is locally asymptotically stable.

(ii) if $R_0 > 1$, then E_f is unstable.

(iii) if $R_0 = 1$, then E_f is linearly stable.

Proof. At the point E_f, the characteristic equation (3.6) can be reduced to

$$(s+d)\left[(s+p+\gamma)\left(s+u+\frac{\beta\lambda}{d}\right)-\frac{k\beta\lambda}{d}e^{-p\tau-s\tau-u\sigma-s\sigma}\right]=0. \tag{3.7}$$

As $d=-s$ demonstrates, the first root of equation (3.7) has a negative root, and equation (3.8) must be used to determine the other roots.

$$(s+p+\gamma)\left(s+u+\frac{\beta\lambda}{d}\right)-\frac{k\beta\lambda}{d}e^{-p\tau-u\sigma-s\tau-s\sigma}=0. \tag{3.8}$$

Equation (3.8) can be written as

$$s^2+s\left(p+\gamma+u+\frac{\beta\lambda}{d}\right)+(p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)\left[1-R_0e^{-s\tau-s\sigma}\right]=0. \tag{3.9}$$

For any $\tau \geq 0$ and $\sigma \geq 0$, when $s=0$, equation (3.9) becomes

$$(p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)(1-R_0)=0.$$

Thus, if $R_0 \neq 1$, $s=0$ is not a solution of (3.8), for any $\tau,\sigma \geq 0$.

Let, $\tau=0$ and $\sigma=0$. Then, from equation (3.9) becomes

$$s^2+s\left(p+\gamma+u+\frac{\beta\lambda}{d}\right)+(p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)(1-R_0)=0. \tag{3.10}$$

Clearly, if $R_0 < 1$,

$$\left(p+\gamma+u+\frac{\beta\lambda}{d}\right)>0 \quad \text{and} \quad (p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)(1-R_0)>0.$$

Therefore, by Ruth Hurwitz criterion, all roots of equation (3.10) have negative real parts. Therefore, if $R_0 < 1$, all the roots of equation (3.7) are negative real parts. Hence, if $R_0 < 1$, the point E_f is locally asymptotically stable.

Next, assume that $\tau > 0, \sigma > 0$, and $s = \omega i (\omega > 0)$, is a pure imaginary root of equation (3.8) [27]. Then, from equation (3.8), we have

$$(\omega i + \gamma + p)\left(\omega i + u + \frac{\beta\lambda}{d}\right) - \frac{k\beta\lambda}{d} e^{-p\tau - u\sigma - i\omega\tau - i\omega\sigma} = 0. \tag{3.11}$$

By separating the imaginary and the real parts of (3.11), we have the following system

$$-\omega^2 + (p+\gamma)\left(u + \frac{\beta\lambda}{d}\right) = \frac{k\beta\lambda}{d} e^{-u\sigma - p\tau} \cos\omega(\tau+\sigma) \tag{3.12}$$

$$\omega\left(p + \gamma + u + \frac{\beta\lambda}{d}\right) = -\frac{k\beta\lambda}{d} e^{-u\sigma - p\tau} \sin\omega(\tau+\sigma) \tag{3.13}$$

From the equations (3.12), (3.13) and (3.1), we have

$$\omega^4 + \left[(p+\gamma)^2 + \left(u + \frac{\beta\lambda}{d}\right)^2\right]\omega^2 + (p+\gamma)^2\left(u + \frac{\beta\lambda}{d}\right)^2 (1 - R_0^2) = 0. \tag{3.14}$$

Clearly equation (3.14) has no positive solution for ω^2 when $R_0 < 1$. Hence, there is no roots $s = i\omega$ for equation (3.8) with $\omega \geq 0$. This implies, the roots of (3.8) do not pass through the imaginary axis. Therefore, if $R_0 < 1$, all roots of equation (3.7) have negative real parts. Hence, from theorem 3.4.1 in [27], the infection-free equilibrium point E_f is locally asymptotically stable.

Conversely, when $R_0 > 1$, it is not difficult to show that equation (3.8) has a real positive root. Letting the equation (3.9) as

$$g(\tau, \sigma, s) = s^2 + s\left(p + \gamma + u + \frac{\beta\lambda}{d}\right) + (p+\gamma)\left(u + \frac{\beta\lambda}{d}\right)\left[1 - R_0 e^{-s\tau - s\sigma}\right]. \tag{3.15}$$

For any $\tau, \sigma \geq 0$, and $R_0 > 1$, we have

$$g(\tau, \sigma, 0) = (p+\gamma)\left(u + \frac{\beta\lambda}{d}\right)(1 - R_0) < 0 \quad \text{and}$$

$$\lim_{s \to +\infty} g(\tau, \sigma, s) \to +\infty.$$

Hence, $g(\tau, \sigma, s) = 0$ has at least one positive root if $R_0 > 1$. Thus if $R_0 > 1$ the infection-free equilibrium point E_f is unstable.

When $R_0 = 1$, from equation (3.9) we have

$$s^2 + s\left(p+\gamma+u+\frac{\beta\lambda}{d}\right) + (p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)\left(1-e^{-s\tau-s\sigma}\right) = 0. \tag{3.16}$$

It is obvious that $s = 0$ is a solution of (3.16).

Further, any other root of (3.16) can be proved to be negative real.

Assume that $s = \alpha_1 + i\alpha_2$ is a root of equation (3.16) for some $\alpha_1, \alpha_2 \geq$ and $\tau, \sigma \geq 0$. Then, by substituting s into (3.16) and separating the imaginary and real parts, we have the following equations.

(3.17)

$$\alpha_1^2 - \alpha_2^2 + \alpha_1\left(p+\gamma+u+\frac{\beta\lambda}{d}\right) + (p+\gamma)\left(u+\frac{\beta\lambda}{d}\right) = (p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)e^{-\alpha_1(\tau+\sigma)}\cos\alpha_2(\tau+\sigma),$$

and

$$2\alpha_1\alpha_2 + \alpha_2\left(p+\gamma+u+\frac{\beta\lambda}{d}\right) = -(p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)e^{-\alpha_1(\tau+\sigma)}\sin\alpha_2(\tau+\sigma). \tag{3.18}$$

By squaring equations (3.17) and (3.18) and adding, we have the inequality,

$$\begin{aligned}\left[\alpha_1^2 - \alpha_2^2 + \alpha_1\left(p+\gamma+u+\frac{\beta\lambda}{d}\right) + (p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)\right]^2 \\ + \left[2\alpha_1\alpha_2 + \alpha_2\left(p+\gamma+u+\frac{\beta\lambda}{d}\right)\right]^2 \leq \left[(p+\gamma)\left(u+\frac{\beta\lambda}{d}\right)\right]^2.\end{aligned} \tag{3.19}$$

Clearly inequality (3.19) cannot be fulfilled, which prompts a logical inconsistency. This implies every roots of the equation (3.16) are negative real except $s = 0$. □

Theorem 3.3. *When $R_0 \leq 1$, the infection-free equilibrium $E_f(\lambda/d, 0, 0)$ of system (1.2) is globally asymptotically stable for any $\tau, \sigma \geq 0$.*

Proof. Let prove Theorem 3.3 under the two cases.

Consider $(x(t), y(t), v(t))$ be any solution of model (1.2) with initial condition (2.1).

Case I: If $ke^{-u\sigma-p\tau} - (p+\gamma) > 0$

Define a Lyapunov functional $V_1(t)$ as follows

$$V_1(t) = \left(x(t) - x_0 - x_0 \ln\frac{x(t)}{x_0}\right) + k_1 y(t) + k_2 v(t) + k_2 I_1 + k_1 J_1, \tag{3.20}$$

where,

$$I_1 = ke^{-u\sigma}\int_{t-\sigma}^{t} y(\theta)d\theta, \quad \text{and} \quad J_1 = \beta e^{-p\tau}\int_{t-\tau}^{t}\frac{x(\theta)v(\theta)}{1+\alpha v(\theta)}d\theta.$$

where k_1 and k_2 are determined later.

For $t \geq 0$, taking the derivative of $V_1(t)$ along the solutions of (1.2), it shows that.

(3.21)
$$\begin{aligned}\dot{V}_1(t) = \left(1-\frac{x_0}{x(t)}\right)\left[\lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \gamma y(t)\right] + k_1\left[\frac{\beta e^{-p\tau}x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - (p+\gamma)y(t)\right] \\ + k_2\left[ke^{-u\sigma}y(t-\sigma) - uv(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right] + k_2 k e^{-u\sigma}\left[y(t)-y(t-\sigma)\right] \\ + k_1\beta e^{-p\tau}\left[\frac{x(t)v(t)}{1+\alpha v(t)} - \frac{x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)}\right]\end{aligned}$$

Substituting $x_0 = \lambda/d$ and taking $(1+k_2) = k_1 e^{-p\tau}$ and $k_1(p+\gamma) = k_2 k e^{-u\sigma}$, equation (3.21) can be derived as follows

$$\dot{V}_1(t) = -\frac{d}{x(t)}(x(t)-x_0)^2 + \frac{\beta x_0 v(t)}{1+\alpha v(t)} + (x(t)-x_0)\frac{\gamma y(t)}{x(t)} - k_2 u v(t). \tag{3.22}$$

From equation (3.22) and (3.1), we have

$$\dot{V}_1(t) \leq -\frac{d}{x(t)}(x(t)-x_0)^2 - \left(\frac{\lambda}{d} - x(t)\right)\frac{\gamma y(t)}{x(t)} + \frac{(R_0-1)(p+\gamma)(ud+\lambda\beta)v(t)}{d(ke^{-p\tau-u\sigma}-(p+\gamma))}. \tag{3.23}$$

Thus, If $R_0 \leq 1$, from (2.8)(see e.g. Theorem 3 in [28]) and when $ke^{-p\tau-u\sigma} - (p+\gamma) > 0$ we have $\dot{V}_1(t) \leq 0$. The equality holds if and only if $x(t) = \frac{\lambda}{d}$, and $v = 0$. By theorem 5.3.1 in [29], let M_1 be the largest invariant subset in $E_1 = \{\psi = (x(t), y(t), v(t)) \in \mathbb{R}^3_+ \mid \dot{V}_1(\psi) = 0\}$. Therefore, from the last equation of (1.2) we get $y = 0$. This implies that $M_1 = \{E_0\}$. By implies of LaSalle's invariance principle, it has that the disease free equilibrium E_f is globally asymptotically steady when $R_0 \leq 1$.

Case II: When $ke^{-u\sigma-p\tau} - (\gamma+p) \leq 0$, Let us define a Lyapunov functional as

$$V_2(t) = e^{p\tau}y(t) + v(t) + \beta\int_{t-\tau}^{t}\frac{x(\theta)v(\theta)}{1+\alpha v(\theta)}d\theta + ke^{-u\sigma}\int_{t-\sigma}^{t}y(\theta)d\theta. \tag{3.24}$$

For $t \geq 0$, taking the derivative of $V_2(t)$ along the solutions of (1.2), equation (3.24) can be derive as follows.

$$\dot{V}_2(t) = \left(ke^{-u\sigma-p\tau} - (p+\gamma)\right)e^{p\tau}y(t) - uv(t). \tag{3.25}$$

Clearly, $\dot{V}_2 \leq 0$ for all $y, v > 0$ when $ke^{-u\sigma-p\tau} - (p+\gamma) \leq 0$. Then, at this point, by a similar argument as above, it is not difficult to show that E_f is globally asymptotically stable. This prove Theorem 3.3. □

3.3. Stability of the chronic infection equilibrium. In this subsection we study the local stability of the chronic infection equilibrium point $E_{ch}(x_1, y_1, v_1)$ by using the characteristic equation of model (1.2) considering three special cases that $\tau = 0, \sigma = 0$, $\tau \geq 0, \sigma = 0$, and $\tau = 0, \sigma \geq 0$ and the global stability of the chronic equilibrium points by using the Barbalat's lemma in [30].

Theorem 3.4. *When $R_0 > 1$, for any $\tau \geq 0, \sigma = 0$ and $\tau = 0, \sigma \geq 0$, the chronic infection equilibrium E_{ch} of system (1.2) is locally asymptotically stable.*

Proof. Let

$$L = \frac{v_1}{(1+\alpha v_1)} \quad \text{and} \quad M = \frac{x_1}{(1+\alpha v_1)^2}$$

Then, from (3.6) the characteristic equation at $E_{ch}(x_1, y_1, v_1)$ can be derived as

$$\begin{aligned} &(s+d+\beta L)\left[(s+\gamma+p)(s+u+\beta M) - k\beta M e^{-s(\sigma+\tau)-u\sigma-p\tau}\right] \\ &+\gamma\left[-\beta L e^{-p\tau-s\tau}(s+u+\beta M) + \beta^2 L M e^{-p\tau-s\tau}\right] \\ &+\beta M\left[k\beta L e^{-s(\sigma+\tau)-u\sigma-p\tau} - \beta L(s+\gamma+p)\right] = 0. \end{aligned} \tag{3.26}$$

Since E_{ch} satisfy system (1.2), equation (3.26) further can be simplified as

$$s^3 + a_2 s^2 + a_1 s + a_0 + (b_1 s + b_0)e^{-s\tau-s\sigma} + (c_1 s + c_0)e^{-s\tau} = 0. \tag{3.27}$$

where,

$$\begin{aligned} a_0 &= u(p+\gamma)(\beta L + d) + (p+\gamma)M\beta d, \\ a_1 &= (p+\gamma)(u+\beta M) + (L\beta + d)(p+\gamma+u) + dM\beta, \\ a_2 &= p+\gamma+u+d+M\beta+L\beta, \\ b_0 &= -d(p+\gamma)\left[\frac{u}{1+\alpha v_1} + \beta M\right], \quad b_1 = -(p+\gamma)\left[\frac{u}{1+\alpha v_1} + \beta M\right], \\ c_0 &= -u\gamma\beta L e^{-p\tau}, \quad c_1 = -\gamma\beta L e^{-p\tau}. \end{aligned}$$

When $\sigma = \tau = 0$, equation (3.27) reduced to the form

$$s^3 + a_2 s^2 + (a_1 + b_1 + c_1)s + (a_0 + b_0 + c_0) = 0, \tag{3.28}$$

and by direct computation, we have

$$a_0+b_0+c_0 = puL\beta + \frac{(p+\gamma)ud\alpha v_1}{1+\alpha v_1} > 0,$$
$$a_1+b_1+c_1 = d(p+\gamma+u) + \frac{(p+\gamma)u\alpha v_1}{1+\alpha v_1} + \frac{\beta(p+u)v_1}{1+\alpha v_1} + \frac{d\beta x_1}{(1+\alpha v_1)^2} > 0.$$

and

$$a_2(a_1+b_1+c_1) - (a_0+b_0+c_0) = (p+\gamma+d+\beta M+\beta L)\left[pL\beta + \frac{(p+\gamma)d\alpha v_1}{1+\alpha v_1}\right]$$
$$+(p+\gamma+d+u+\beta L+\beta M)\left[(d+L\beta)u + d\beta M + \frac{(p+\gamma)(d+u\alpha v_1)}{1+\alpha v_1}\right] > 0.$$

Therefore, according to the Routh-Hurwitz criterion, any root of equation (3.28) has negative real part for $\tau = 0$ and $\sigma = 0$. Hence, for $\tau = \sigma = 0$, the chronic infection equilibrium E_{ch} of system (1.2) is locally asymmetrically stable.

As a second case, consider $\sigma = 0$ and $\tau \geq 0$. Then equation (3.27) can be written as

$$s^3 + a_2s^2 + a_1s + a_0 + [(b_1+c_1)s + (b_0+c_0)]e^{-s\tau} = 0. \tag{3.29}$$

Let $s = i\omega$ ($\omega > 0$) is the purely imaginary root of equation (3.29). Then, by substituting S into (3.29) and separating the imaginary and real parts, we obtain following two equations

$$\omega(b_1+c_1)\sin(\omega\tau) + (b_0+c_0)\cos(\omega\tau) = a_2\omega^2 - a_0 \tag{3.30}$$

$$\omega(b_1+c_1)\cos(\omega\tau) - (b_0+c_0)\sin(\omega\tau) = \omega^3 - a_1\omega \tag{3.31}$$

By squaring equation (3.30) and (3.31), and adding together we have

$$(\omega^3)^2 + (a_2^2 - 2a_1)(\omega^2)^2 + [a_1^2 - 2a_2a_0 - (b_1+c_1)^2]\omega^2 + [a_0^2 - (b_0+c_0)^2] = 0. \tag{3.32}$$

Let, $m_3 = a_2^2 - 2a_1, m_2 = a_1^2 - 2a_2a_0 - (b_1+c_1)^2, m_1 = a_0^2 - (b_0+c_0)^2$ and $u > u/(1+\alpha v_1)$. Then by direct calculation, it can be show that

$$m_3 = (u+\beta M)^2 + 2\beta^2 ML + (p+\gamma)^2 + (d+\beta L)^2 > 0,$$
$$m_2 > \frac{(p+\gamma)^2 u\alpha v_1}{1+\alpha v_1}\left[2\beta M + \frac{u(2+\alpha v_1)}{1+\alpha v_1}\right] + 2ud\beta M(d+\beta L) + (d+\beta L)^2(pr+u^2)$$
$$+ (d\beta M)^2 + \gamma^2(d+2d\beta L) + (p+\gamma)\left[2p\beta^2 ML + p(d+\beta L)^2 + 2u\beta L\gamma\right]$$
$$+ \gamma^2\beta^2 L^2(1-e^{-2p\tau}) + 2\gamma\beta L(p+\gamma)(u+\beta M)(1-e^{-p\tau}) > 0.$$

$$m_1 = \left[(p+\gamma)\left(u(L\beta+d)+2d\beta M+\frac{du}{1+\alpha v_0}\right)+uL\gamma\beta e^{-p\tau}\right] \left[puL\beta+\frac{(p+\gamma)du\alpha v_1}{1+\alpha v_1}+uL\gamma\beta(1-e^{-p\tau})\right] > 0.$$

Hence, based on the Routh-Hurwitz criterion, when $\tau \geq 0$, (3.32) has no positive real roots for ω^2. Consequently, this implies that all roots of equation (3.29) have negative real parts. That is, if $R_0 > 1$, the chronic disease equilibrium E_{ch} in model (1.2) is locally asymptotically stable [27].

As the third case, when $\sigma \geq 0$ and $\tau = 0$, equation (3.27) can be written as

$$s^3 + a_2 s^2 + (a_1 + c_1)s + (a_0 + c_0) + (b_1 s + b_0)e^{-s\sigma} = 0. \tag{3.33}$$

Let $s = i\omega(\omega > 0)$ is the purely imaginary root of equation (3.33). Then by substituting S into (3.33) and separating imaginary and real parts of the equation, we obtain following two equations.

$$b_1\omega\cos(\omega\sigma) - b_0\sin(\omega\sigma) = \omega^3 - (a_1+c_1)\omega \tag{3.34}$$

$$b_1\omega\sin(\omega\sigma) + b_0\cos(\omega\sigma) = a_2\omega^2 - (a_0+b_0) \tag{3.35}$$

By adding the squares of both sides of equations (3.34) and (3.34), we have

(3.36)

$$(\omega^3)^2 + [a_2^2 - 2(a_1+c_1)](\omega^2)^2 + [(a_1+c_1)^2 - 2a_2(a_0+c_0) - b_1^2]\omega^2 + (a_0+c_0)^2 - b_0^2 = 0.$$

Let, $m_4 = a_2^2 - 2(a_1+c_1), m_5 = (a_1+c_1)^2 - 2a_2(a_0+c_0) - b_1^2$, and $m_6 = (a_0+c_0)^2 - b_0^2$. Then by direct calculation, it can be show that

$$m_4 = (u+\beta M)^2 + 2\beta^2 ML + (p+\gamma)^2 + (d+\beta L)^2 + 2\gamma\beta L > 0$$

$$m_5 > \frac{(a+\gamma)^2 u\alpha v_1}{1+\alpha v_1}\left[2\beta M + \frac{u(2+\alpha v_1)}{1+\alpha v_1}\right] + u^2(d+\beta L)^2 + 2\beta d^2 uM + 2\gamma\beta Lu^2 + (d\beta M)^2 + 2a\beta^2 ML(a+\gamma) + (d^2+\beta^2 L^2)(a^2+\gamma^2) + 2ad[\gamma d + L\beta(a+\gamma)] > 0$$

$$m_6 = \left[pu(d+\beta L) + u\gamma d + d\beta M(p+\gamma) + d(p+\gamma)\left(\frac{u}{1+\alpha v_1} + \beta M\right)\right] \left[pu\beta L + \frac{d(p+\gamma)\alpha v_1}{1+\alpha v_1}\right] > 0$$

Again, based on the Routh-Hurwitz criterion, (3.32) has no positive real roots for ω^2 when $\sigma \geq 0$. Consequently, this implies that all roots of equation (3.29) have negative real parts. That is, if $R_0 > 1$, the chronic disease equilibrium E_{ch} in model (1.2) is locally asymptotically stable [27]. □

Theorem 3.5.

(i) If $R_0 \leq 1$, then the infection free equilibrium E_f is globally asymptotically stable.

(ii) If $R_0 > 1$, then the chronic infection equilibrium E_{ch} is globally asymptotically stable.

Proof. Let $X(t) = (x(t), y(t), v(t))$ be the solution of system (1.2). Then, from the Proposition 2.2, $X(t)$ has a finite limit as $t \to +\infty$. Therefore, we consider

$$\lim_{t\to+\infty} X(t) = (x^*, y^*, v^*).$$

According to the Barbalat's lemma[30], we know that

$$\lim_{t\to+\infty} \dot{X}(t) = \mathbf{0}.$$

Hence, from system (1.2), the point (x^*, y^*, v^*) is an equilibrium point.

From Theorem 3.1, we have

$$\lim_{t\to+\infty} X(t) = E_f \quad \text{or} \quad \lim_{t\to+\infty} X(t) = E_{ch}$$

If $R_0 < 1$, the chronic infection equilibrium point E_{ch} does not exits. Thus $\lim_{t\to+\infty} X(t) = E_f$. From the (iii) of Theorem 3.2, if $R_0 = 1$, E_f is linearly stable and then, $\lim_{t\to+\infty} X(t) = E_f$. If $R_0 > 1$, from the (ii) of Theorem 3.2, E_f is unstable. Hence, $\lim_{t\to+\infty} X(t) = E_{ch}$. □

4. PERMANENCE

In this subsection, we will investigate the uniform persistence of model (1.2) with given initial values (2.1). Biologically, the uniform persistence or permanence suggests that the virus $v(t)$ and infected cells $y(t)$ not possible totally removed from the body and will ultimately continue. To prove the system (1.2) is persistence, here we introduce persistence theory introduced in [31] by Hale. Moreover, we express the states of Theorem 5.1.1 in [32] and have used the methods and closely agree with the thoughts of [13, 33] and [34] on evidence for persistence.

To continue, we present the terminology and notation as follows. Let the Banach space of continuous functions which composed with sup-norm $X = C\left([-\zeta,0],\mathbb{R}^3_+\right)$ is mapping the interval $[-\zeta,0]$ into $\mathbb{R}^3_+$, $X^0 = \{(\phi_1,\phi_2,\phi_3) \in X : \phi_2(\theta) > 0, \phi_3(\theta) > 0, \text{and} \theta \in [-\zeta,0]\}$, and $\partial X = X/X^0 = \{(\phi_1,\phi_2,\phi_3) \in X : \phi_2(\theta) = 0, or\, \phi_3(\theta) = 0, \theta \in [-\zeta,0]\}\} = X_0$. For $t \geq 0.$, let $P(t)$ be the set of solutions operators for model (1.2). Defined $\omega-$ limit set as $\omega(x) = \{y \in X | \text{there is a sequence} t_n \to \infty \text{as} n \to \infty \text{with} P(t_n)x \to y \text{as} n \to \infty\}$. Then, we refer Theorem 4.2 in [31].

Lemma 4.1. *Assume that we have*

(i) $X^0 \in X$ *is a open set with* $X^0 \bigcap X_0 = \emptyset$ *and* $X^0 \bigcup X_0 = X$,

(ii) $P(t)$ *satisfy* $P(t) : X_0 \to X_0$, $P(t) : X^0 \to X^0$, *and point dissipative in* X,

(iii) $P(t)$ *is asymptotically smooth,*

(iv) If Y_2 *is the global attractor of* $P(t)$ *limited to* X_0 *and* $N = \bigcap_{i=1}^{k} N_i$, *then*

$\Omega_2 = \bigcup_{x \in Y_2} \omega(x)$ *is isolate and has acyclic covering N,*

(v) for each $N_i \in N, W^s(N_i) \bigcap X^0 = \emptyset$, *where* W^s *is stable set.*

Then we have a uniform repeller $P(t)$ *with respect to* X_0. *That is, there exists an* $\eta > 0$ *such that for arbitrary* $x \in X_0$, $\liminf_{t \to +\infty} d(P(t), X_0) \geq \eta$.

Theorem 4.1. *If* $R_0 > 1$, *then model (1.2) is uniformly persistent for any* $\sigma, \tau \geq 0$ *with the condition (2.1). i.e there is any* $\xi > 0$ *such that for any solution* $(x(t), y(t), v(t))$ *of model (1.2) satisfy* $\liminf_{t \to +\infty} x(t) > \xi$, $\liminf_{t \to +\infty} y(t) > \xi$ *and* $\liminf_{t \to +\infty} v(t) > \xi$.

Proof. By Theorem 2.1 and Proposition 2.2, it is straightforward to see that $(i) - (iii)$ of Lemma 4.1 always hold. Consequently, we only have to verify the last two conditions of the Lemma 4.1. For that we can define a set M_∂ as

$$M_\partial = \{\phi \in C\left([-\zeta,0],\mathbb{R}^3_+\right) : P(t)\phi \text{ satisfies model (1.2) and} P(t)\phi \in \partial X \text{ for all} t \geq 0\}.$$

First we say the set $M_\partial = \{(\frac{\lambda}{d},0,0)\}$. Assume that $P(t) \in M_\partial$, for all $t \geq 0$. Then it is enough to show that $y(t) = 0$ and $v(t) = 0$ for all $t \geq 0$. We then use contradiction to prove this claim. suppose that there exists $t_1 > 0$ such that (A). $y(t_1) > 0$, $v(t_1) = 0$; or (B). $y(t_1) = 0$, $v(t_1) > 0$.

For case (A), from the last equation of system (1.2), we have

$$\dot{v}(t)\mid_{t=t_1} > 0.$$

Hence, there exist arbitrarily small constant ε_1 such that $v(t) > 0$ for all $t \in (t_1, t_1+\varepsilon_1)$. Then again, from $y(t_1) > 0$, we have a arbitrarily small constant $\varepsilon_0 (0 < \varepsilon_0 < \varepsilon_1)$. Thus, we have $x(t) > 0, y(t) > 0$ for $\forall t \in (t_1, t_1+\varepsilon_0)$, which lead us to contradiction with the assumption that $(x(t), y(t), v(t)) \in M_\partial$ for $\forall t \geq 0$. Similarly it is easy to show that case (B) does not exists.

Let $\Omega_2 = \bigcup_{x\in Y_2} \omega(x)$, where Y_2 is the global attractor of $P(t)$ restricted to the set ∂X. Now we need to show that $\Omega_2 = \{E_f\}$. Indeed, it follows from $\Omega_2 \subseteq M_\partial$ and using the first equation of system (1.2), Clearly $\lim_{t\to+\infty} x(t) = \frac{\lambda}{d}$. As a result, it is clear that $\{E_f\} \in X$ is a unique invariant set.

Next, we need to prove that $W^s(E_f) \bigcap X^0 = \emptyset$. To prove this result, we assume the contradiction. Suppose $(x(t), y(t), v(t)) \in X^0$ is a positive solution for system (1.2) such that

$$\lim_{t\to\infty} x(t) = x_0 = \frac{\lambda}{d}, \quad \lim_{t\to\infty} y(t) = 0, \text{ and } \quad \lim_{t\to\infty} v(t) = 0. \tag{4.1}$$

Then, for any small constant $\varepsilon > 0$, we have positive constant $t_0 > 0$, such that

$$\frac{\lambda}{d} - \varepsilon < x(t) < \frac{\lambda}{d} + \varepsilon, \quad 0 < y(t) < \varepsilon, \text{ and } \quad 0 < v(t) < \varepsilon \text{ for all } t \geq t_0.$$

Thus, for the selected constant ε, from model (1.2) that for $t \geq t_0 + \tau$ and $t \geq t_0 + \sigma$, we have

$$\begin{aligned} \dot{y}(t) &\geq \frac{e^{-p\tau}\beta(\frac{\lambda}{d} - \varepsilon)v(t-\tau)}{1+\alpha\varepsilon} - (p+\gamma)y(t), \\ \dot{v}(t) &\geq ke^{-u\sigma}y(t-\sigma) - uv(t) - \frac{\beta(\frac{\lambda}{d}+\varepsilon)v(t)}{1+\alpha\varepsilon}. \end{aligned} \tag{4.2}$$

System (4.2) follows the quasi-monotone structure since the right hand sides of the first and second equations of system (4.2) is increasing with the functions $v(t-\tau)$ and $y(t-\sigma)$ (see e.g. [13]).

Consider the following system of differential equations to apply the comparison principle.

$$\begin{aligned} \dot{u_1}(t) &= \frac{e^{-p\tau}\beta(\frac{\lambda}{d} - \varepsilon)u_2(t-\tau)}{1+\alpha\varepsilon} - (p+\gamma)u_1(t), \\ \dot{u_2}(t) &= ke^{-u\sigma}u_1(t-\sigma) - uu_2(t) - \frac{\beta(\frac{\lambda}{d}+\varepsilon)u_2(t)}{1+\alpha\varepsilon}. \end{aligned} \tag{4.3}$$

with the initial condition $u_1(t) = y(t)$, $u_2(t) = v(t)$, $\forall t \in [t_0, t_0 + \zeta]$, where $\zeta = max\{\tau, \sigma\}$. It is obvious that system (4.3) has non-negative solutions $(u_1(t), u_2(t))$.

To verify the states of Theorem 5.1.1 in [32], let us follows the notation of Theorem 5.1.1 and define as $(f_1(t,\phi_2), f_2(t,\phi_3)) = (y(t,\phi_2), v(t,\phi_3))$ and $(g_1(t,\phi_2), g_2(t,\phi_3)) = (u_1(t,\phi_2), u_2(t,\phi_3))$. From Theorem 2.1, we have that $(y(t), v(t))$ is bounded, Hence for the systems (4.2) and (4.3), it is obvious $f_1(t,\phi_2), f_2(t,\phi_3))$ and $(g_1(t,\phi_2), g_2(t,\phi_3))$ are continuous and Lipschitz on each compact subset of X, and also $f_1(t,\phi_2), f_2(t,\phi_3))$ satisfies the condition Q: at any time $\phi \leq \psi$ and $\phi_i(0) = \psi_i(0)$ hold for some i, then $f_i(\phi) \leq f_i(\psi)$[32]. Therefore, model (4.2), satisfy all the conditions of Theorem 5.1.1 in [32]. Hence, according to the comparison principle (Theorem 5.1.1 in [32]), The solutions $(u_1(t), u_2(t))$ of system (4.3) are coverage to $(0,0)$ with the given initial conditions as we have assumed that $(y(t), v(t))$ converge to $(0,0)$ as $t \to \infty$.

Define

$$\begin{aligned} V_3(t) = u_1(t) + \frac{\beta e^{-p\tau}(\frac{\lambda}{d} - \varepsilon)}{u(1+\alpha\varepsilon) + \beta(\frac{\lambda}{d} + \varepsilon)} u_2(t) + \frac{\beta e^{-p\tau}(\frac{\lambda}{d} - \varepsilon)}{1 + \alpha\varepsilon} \int_{t-\tau}^{t} u_2(\theta) d\theta \\ + \frac{k\beta e^{-p\tau - u\sigma}(\frac{\lambda}{d} - \varepsilon)}{u(1+\alpha\varepsilon) + \beta(\frac{\lambda}{d} + \varepsilon)} \int_{t-\sigma}^{t} u_1(\theta) d\theta. \end{aligned} \tag{4.4}$$

Then, from the solutions $\lim_{t\to\infty}(u_1(t), u_2(t)) \to (0,0)$, we have that

$$\lim_{t \to +\infty} V_3(t) = 0. \tag{4.5}$$

Taking the derivative of $V_3(t)$ along the solutions of model (4.3), we have

$$\dot{V}_3(t) = \left[\frac{k\beta e^{-p\tau - u\sigma}(\frac{\lambda}{d} - \varepsilon)}{u(1+\alpha\varepsilon) + \beta(\frac{\lambda}{d} + \varepsilon)} - (p + \gamma) \right] u_1(t). \tag{4.6}$$

Since $R_0 > 1$, it is possible to choose sufficiently small constant for ε, such that

$$\frac{k\beta e^{-p\tau - u\sigma}(\frac{\lambda}{d} - \varepsilon)}{u(1+\alpha\varepsilon) + \beta(\frac{\lambda}{d} + \varepsilon)} - (p + \gamma) > 0. \tag{4.7}$$

Consequently, $V_3(t)$ tends to either a positive constant value or infinity as $t \to \infty$. This is a contradiction to equation (4.5). Hence, we have $W^s(E_f) \bigcap X^0 = \emptyset$. Therefore, from the Lemma 4.1, we can get some constant $\xi_0 > 0$ such that

$$\liminf_{t\to+\infty} y(t) > \xi_0, \text{ and } \liminf_{t\to+\infty} v(t) > \xi_0.$$

Further, using the first equation of model (1.2), we have [13]

$$\dot{x}(t) \geq \lambda - \left(d + \frac{\beta}{\alpha}\right) x(t).$$

It implies that,

$$\liminf_{t \to +\infty} x(t) \geq \frac{\alpha\lambda}{d\alpha + \beta}.$$

This completes the proof of Theorem (4.1). □

5. NUMERICAL SIMULATIONS

The purpose of this section is to show that the theoretical results that we obtained in Sections (3) and (4) are valid, by using the parameter values that have been reported in the literature and are shown in Table 1.

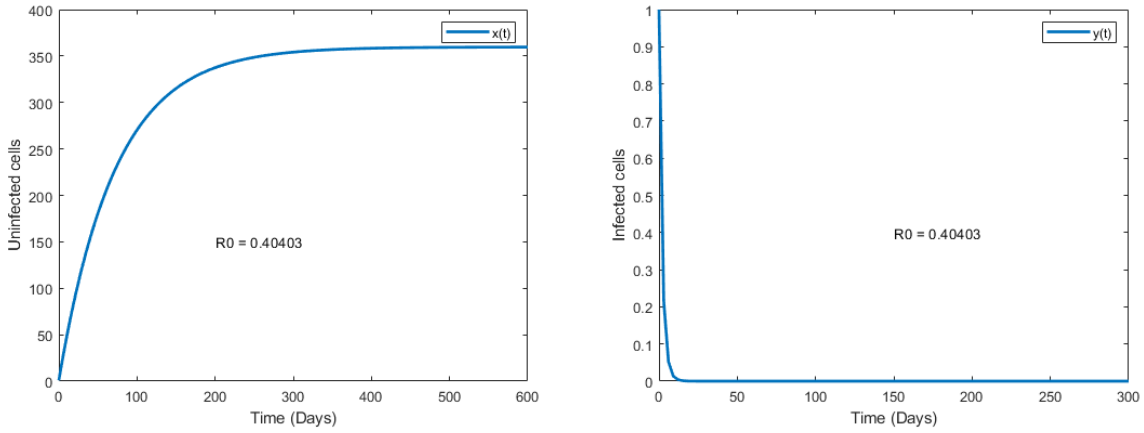
TABLE 1. Parameter values used for numerical simulation.

Parameter	Value	Case I	Case II	Case III	Case IV	Case V	source
λ	05 mm^{-3}	-	-	-	-	-	[35]
d	0.0139 day^{-1}	-	-	-	-	-	[30, 36]
β	0.00024 virons	-	-	-	-	-	[30, 36]
γ	0.01	-	-	-	-	-	[30, 36, 19]
α	0.0001	-	-	-	-	-	Assumed
p	0.5 day^{-1}	-	-	-	-	-	[30, 36, 19]
k	60 day^{-1}	-	-	-	-	-	[36]
u	3 day^{-1}	-	-	-	-	-	[30, 36]
τ	days	5	0	1.6	1.300107	0.9	variable
σ	days	0	0.9	1.2	0.94789	0.5	variable

First, we take that $\tau = 1.6$ and $\sigma = 1.2$ and then the numerical simulation is given that $R_0 = 0.404026 < 1$. Then according to Theorem 3.3, it has shown that the infection free equilibrium $E_f(\lambda/d, 0, 0) \equiv (359.7122, 0, 0)$ is globally asymptotically stable if $R_0 < 1$ for any $\tau, \sigma \geq 0$. The Figures 1 and 2 clearly demonstrate this conclusion. If we chose $\tau = 1.300107$ and $\sigma = 0.94789$, then the reproduction number $R_0 = 1.000000$, and by the Figure 3 verify the

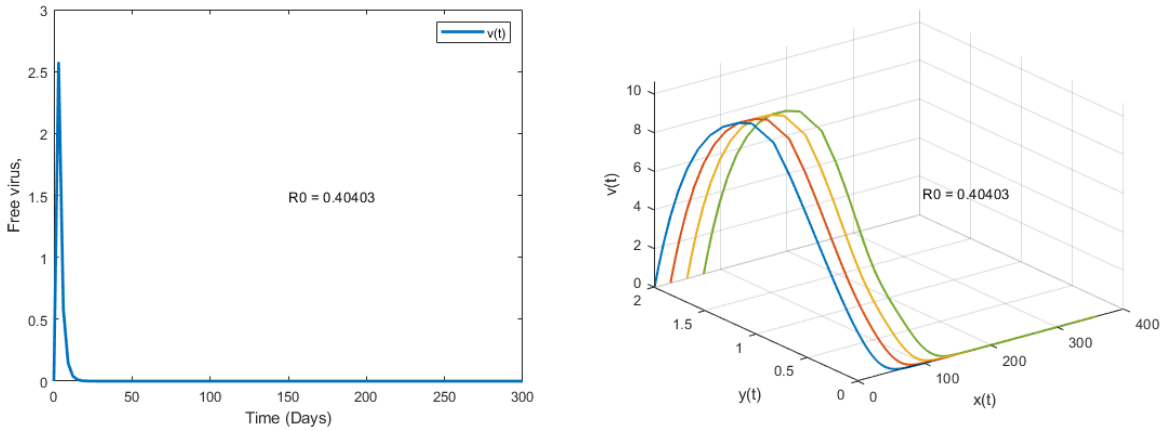
theoretical result given in Theorem 3.3. If we substitute $\tau = 0.9$ and $\sigma = 0.5$, we have $R_0 = 4.681993 > 1$, and the chronic infection equilibrium point is $E_{ch}(76.7880, 4.9790, 220.8676)$. When $\tau = 5, \sigma = 0$ and $\tau = 0, \sigma = 0.9$, the the basic reproduction number $R_0 = 2.7012 > 1$ and $R_0 = 2.2116 > 1$ and the chronic infection equilibrium $E_{ch}(132.1136, 0.5100, 100.9454)$ and $E_{ch}(161.2944, 5.5160, 73.2035)$ respectively. Then the conditions of Theorem 3.4 and Theorem 3.5 are satisfied and this is numerically confirmed by Figures 4, 5 and Figure 6.

It is clear that time lag τ and σ both affect the reproduction rate $R_0 = \frac{\lambda\beta k e^{-u\sigma - p\tau}}{(p+\gamma)(ud+\lambda\beta)}$. When $\sigma = 0$, as shown in figure (7a), R_0 decreases as τ increases. Further, $R_0 < 1$ when τ is greater than 7 and $\sigma = 0$. Consequently, the virus is eliminated from the system. Similarly, as shown in Figure (7b) R_0 decreases when σ increases and $\tau = 0$. Further, (7b) show that, if $\sigma \geq 1.2$, $R_0 \leq 1$. Moreover, Figure 8 shows that sufficiently large τ and σ reduce the reproductive rate. Hence, it is clear that both τ and σ contribute greatly to the removal of the virus from the system.



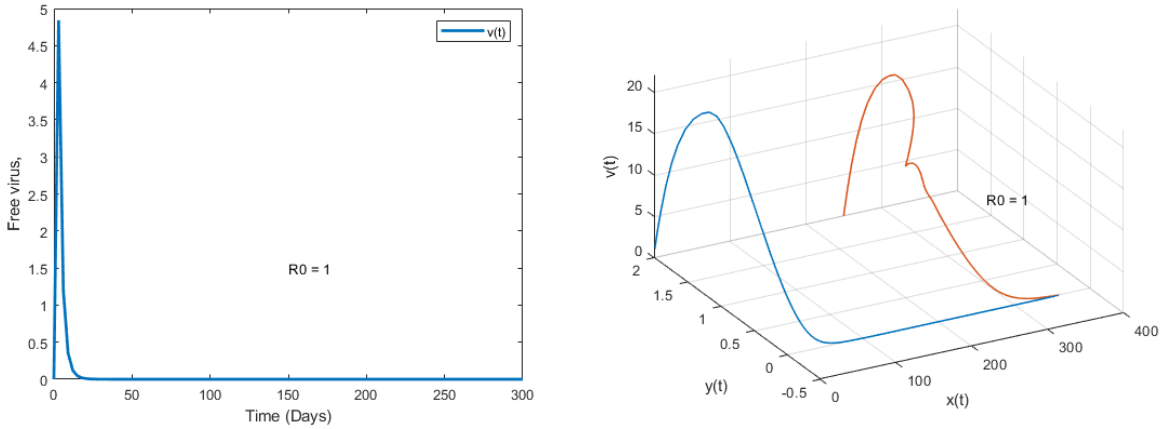
(A) (B)

FIGURE 1. Dynamics of uninfected and infected cells for system (1.2) with parameter values Case III in Table 1, and infection-free equilibrium point $E_0(359.7122, 0, 0)$.



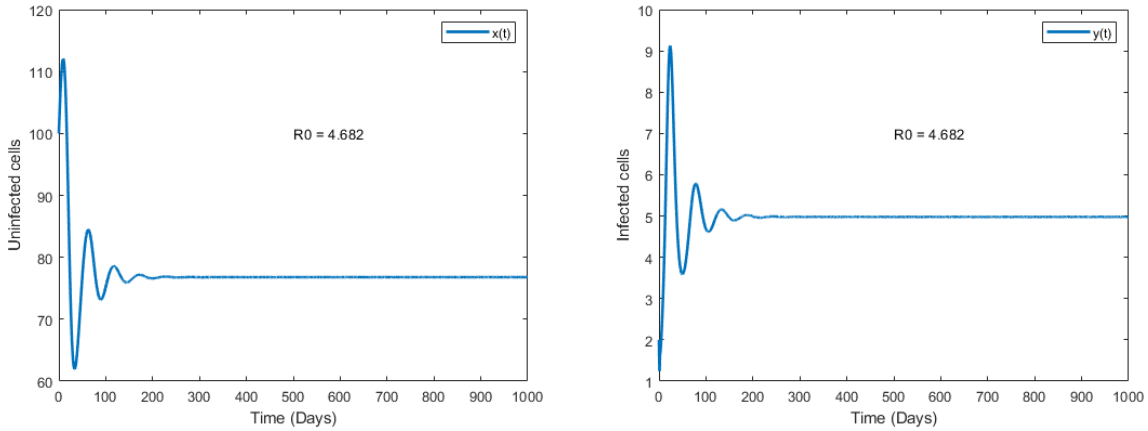
(A) (B)

FIGURE 2. Free-virtual dynamics and phase space for system (1.2) with parameter values Case III in Table 1, and infection-free equilibrium point $E_f(359.7122, 0, 0)$.



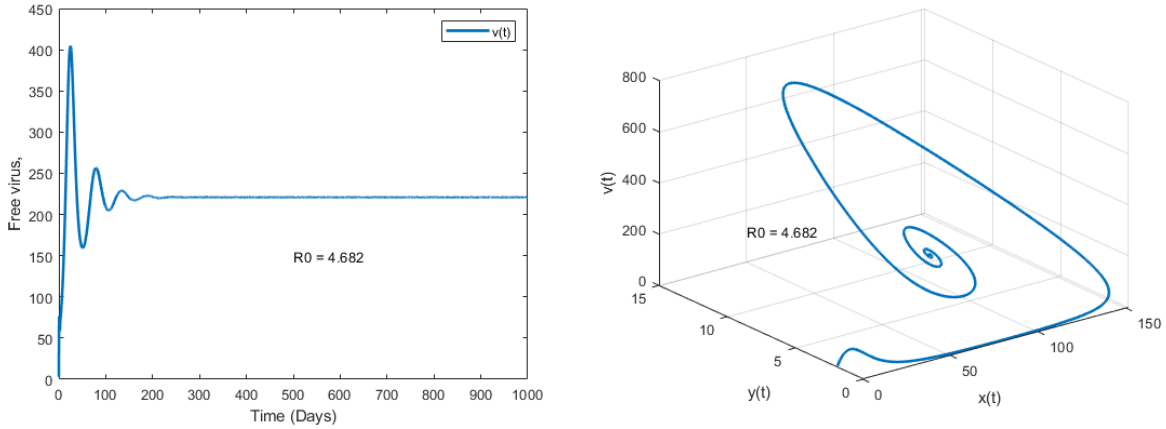
(A) (B)

FIGURE 3. Free-virtual dynamics and phase space for system (1.2) with parameter values Case IV in Table 1, and infection-free equilibrium point $E_f(359.7122, 0, 0)$.



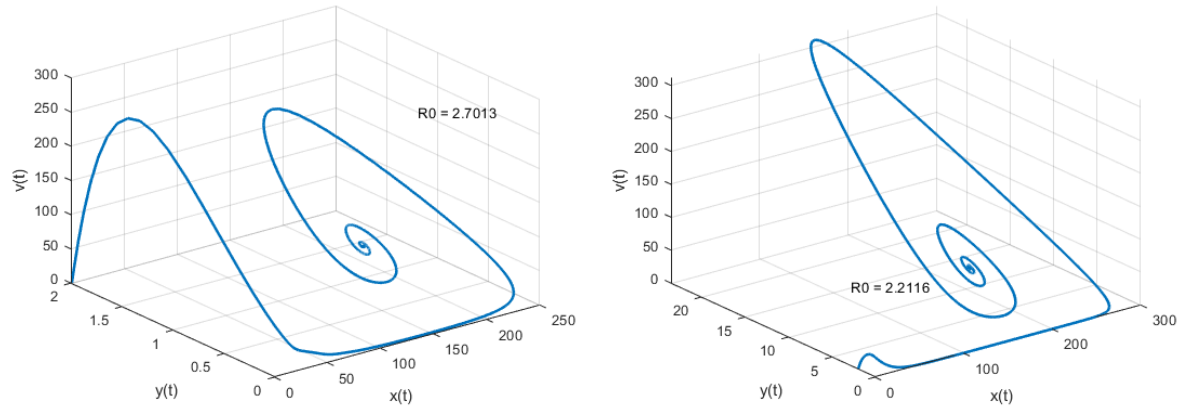
(A) (B)

FIGURE 4. Dynamics of uninfected and infected cells for system (1.2) with parameter values Case V in Table 1, and infection equilibrium point $E_{ch}(76.7880, 4.9790, 220.8676)$.



(A) (B)

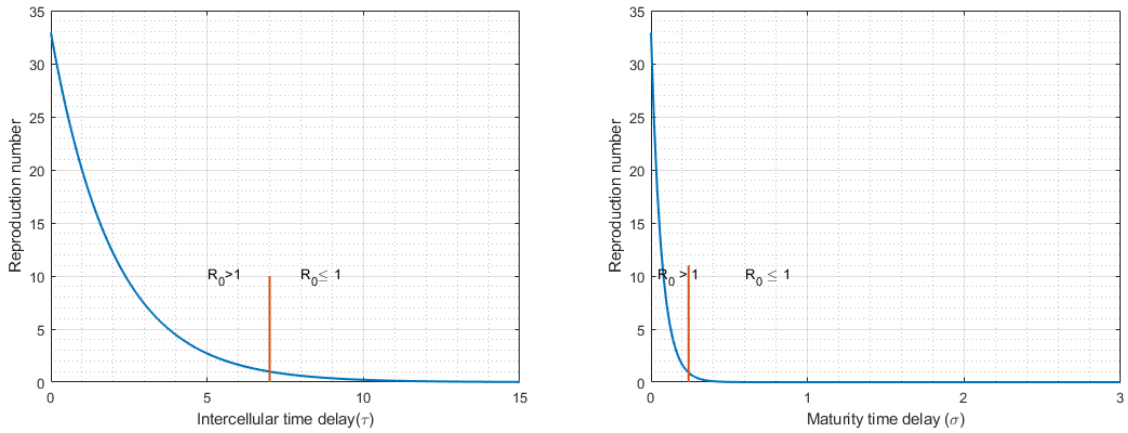
FIGURE 5. Dynamics of free-virus and phase space for system (1.2) with parameter values Case V in Table 1, and infection equilibrium point $E_{ch}(76.7880, 4.9790, 220.8676)$.



(A) Phase diagram when $\sigma = 0$.

(B) Phase diagram when $\tau = 0$.

FIGURE 6. Phase diagram for system (1.2) with parameter values Case I and Case II in Table 1, and the infection equilibrium point are $E_{ch}(132.1136, 0.5100, 100.9454)$ and $E_{ch}(161.2944, 5.5160, 73.2035)$ respectively.



(A) basic reproduction number R_0 as τ increasing ($\sigma = 0$)

(B) basic reproduction number R_0 as σ increasing ($\tau = 0$)

FIGURE 7. Dynamics of the basic reproductive number R_0 when τ and σ increase.

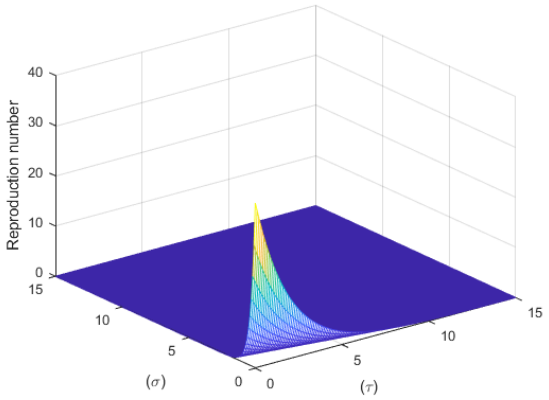


FIGURE 8. Dynamics of basic reproductive number R_0 as both σ and τ increasing.

6. CONCLUSION

In this article we presented and investigated a novel HIV-1 virus dynamics model with saturation infection rate by incorporating the absorption effect, maturation time delay (σ), intracellular time delay (τ) and cure rate into the model. If $R_0 \leq 1$ and $R_0 > 1$, the local stability of the each infection-free equilibrium E_f and the chronic infection equilibrium E_{ch} of the model has fully confirmed by considering the characteristic equation of the system (1.2) in Theorem 3.2 and Theorem 3.4, respectively. Further, if $R_0 \leq 1$, in Theorem 3.3, it has been shown that the E_f is globally stable for any time delay $\sigma, \tau \geq 0$, by using the appropriate Lyapunov function and Lassalle's invariance principle and it further has been verified by using the Barbalat's lemma in Theorem 3.5. In this case, the virus will be removed from the system by activating the immune system of the body or giving external medical treatment, the illness will be cured after some time.

If R_0 of the model is greater than unity, then E_f become unstable (Theorem 3.3) and E_{ch} is locally asymptotically stable (Theorem 3.4). Further it has been shown in Theorem 3.5 chronic infection equilibrium E_{ch} is globally asymptotically stable. In this condition, the infection is chronic and persistent, it biologically means that the host cannot control the infection with drugs or the immune system. In Section (4), it has been confirmed that model (1.2) is uniformly persistence for any $\sigma, \tau \geq 0$, if $R_0 > 1$. Numerical simulations obviously propose that the

chronic infection equilibrium of model(1.2) is globally asymptotically steady if $R_0 > 1$. Figure 8 shows that we can choose sufficiently large enough σ and τ that to satisfy the condition $R_0 \leq 1$ if all other parameters remain constant, which causes the virus to be cleaned out.

Finally, We can reach the following conclusion: A sufficiently large σ and τ can eliminate the virus from the system, and both σ and τ play a vital part within the viral contamination handle. Hence, This research finding may open a new window to think about a new method to increase the maturation time of the virus and to increase the intracellular time which may cause to control or cure the disease.

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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